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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,737	CHOPRA ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/03; 4/19/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-30 are pending in the application.

[2] Applicants' amendment to the claims, filed August 02, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicants' amendment to the specification, filed August 02, 2004, is acknowledged.

[4] Receipt of a sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, and a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, all filed August 02, 2004, is acknowledged. Errors were detected in the CRF of this sequence listing. See the Office Communication and Error Report mailed September 27, 2004.

[5] Receipt of a sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, and a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, all filed October 20, 2004, is acknowledged.

[6] It is noted that the amendment filed August 02, 2004 does not comply with the requirements of 37 CFR 1.121. The status identifiers of claims 1-8 and 28-30 should be listed as "Withdrawn." Applicants are advised to use the proper status identifier for non-elected claims.

Election/Restriction

[7] Applicants' election without traverse of Group III, claims 9-27, filed August 02, 2004, is acknowledged.

[8] Claims 1-8 and 28-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 02, 2004.

Information Disclosure Statement

[9] All references cited in the information disclosure statements (IDSs) filed October 29, 2003 and April 19, 2002 have been considered by the examiner. A copy of each IDS is attached to the instant Office action.

Priority

[10] Applicants' claim to domestic priority under 35 U.S.C. § 119(e) to US provisional application 60/234,576, filed September 22, 2000, is acknowledged. The claimed invention finds support in the provisional application.

Sequence Compliance

[11] The instant application contains at least one nucleic acid and/or amino acid sequence that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Applicants have satisfied the

requirements for sequence compliance, *i.e.,* the application contains a computer readable form (CRF) of the sequence listing, a paper copy thereof, a statement that the CRF and paper copy of the sequence listing are identical, and, as the sequence listing is a substitute sequence listing, a statement that the paper copy of the substitute sequence listing contains no new matter. See papers filed October 20, 2004.

Drawings

[12] The drawings are objected to because Figure 1 is not numbered in accordance with 37 CFR 1.84(u)(1), which states, "[p]artial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by a capital letter." A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification/Informalities

[13] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: --Method for Identifying Agents that Interact with Beta-Site APP Cleaving Enzyme (BACE) by Computer Modeling--.

Claim Objections

[14] Claims 12, 16-20, and 24-27 are objected to in the recitation of "APP." Abbreviations, unless otherwise obvious should not be recited in the claims without at least once reciting the entire phrase, *i.e.*, "beta-amyloid precursor protein" for which the abbreviation is used (see p. 5, ¶ [0017] of the instant specification). Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[15] Claim(s) 9-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 9 (claims 10-11 dependent therefrom), 12 (claims 13-14 and 17-18 dependent therefrom), 15-16, 19, 20 (claims 21-22 and 25-26 dependent therefrom), 23-24, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The active method steps of the claims, *i.e.*, parts a) and b) of claims 9, 12, 15, 20, and 23 fail to recite a data processing method in which: 1) the coordinate data of the 3-D molecular model of Figure 1 is input in a data structure such that the interatomic distances between the atoms of the protein structure of Figure 1 are easily retrieved, and 2) the distances between hydrogen-bonding heteroatoms of

different candidate compounds and the heteroatoms that form the binding pocket in the 3-D molecular model, *e.g.,* those active site amino acids as listed at Table 1 at p. 21 of the specification, are compared thereby allowing the identification of those candidate compounds which would theoretically form the most stable complexes with the 3-D molecular model binding pocket of the protein of Figure 1, based on optimal hydrogen bonding between the two structures. Regarding claims 12, 15, 20, and 23, it is noted that it is unclear as to how one designs an agent as recited in parts b) of the claims. Also, it is unclear as to how one is able to "determine the effect the agent has on the APP binding protein or peptide" by merely "contacting" the agent with the APP binding protein or peptide as recited in claims 16 and 24. Claims 12 (claims 13-14 and 17-18 dependent therefrom), and 20 (claims 21-22 and 25-26 dependent therefrom) are further incomplete as the active method steps of claims 12 and 20 do not achieve the desired result of "identifying an agent that interacts with an active site..."

See particularly Case 7 of the "Report on comparative study on protein 3-dimensional (3-D) structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" at www.uspto.gov/web/tws/wm4/wm4_index.htm.

[b] Claims 9 (claims 10-11, dependent therefrom), 12 (claims 13-15 dependent therefrom), 16-19, 20 (claims 21-23 dependent therefrom), and 24-27 are indefinite in the recitation of "BACE," "APP binding protein or peptide," and "APP" as it is unclear as to the scope of proteins that are considered to be "BACE," "APP binding protein or peptide," or "APP" polypeptide. While it is noted the specification defines "BACE," "APP binding protein or peptide," and "APP" at pp. 5-6 of the specification, it remains unclear

from these "definitions" as to the scope of intended "BACE," "APP binding protein or peptide," or "APP" polypeptides. In this case, the specification fails to disclose the characteristics of a "BACE" or an "APP binding protein or peptide" that would distinguish a "BACE" or an "APP binding protein or peptide" from other polypeptides that have the ability to cleave APP at residue 671 or bind APP and have an APP binding site, respectively. Also, regarding "APP," it is unclear as to the scope of proteins that are encompassed as "having the amino acid sequence deposited with Swiss Prot under accession number CAA31830, including conservative substitutions" as sequences disclosed in sequence databases are often revised and/or updated and further, it is unclear as to those substitutions that are considered to be "conservative substitutions" thereof. It is suggested that applicants clarify the meaning of the terms "BACE," "APP binding protein or peptide," and "APP."

[c] It is not clear as to whether the methods of claims 16, 19, 24, and 27 are conducted *in vitro* or *in silico.* It is suggested that applicants clarify the meaning of the claims. For purposes of examination, the claims have been interpreted as though the additional methods steps recited in claims 16, 19, 24, and 27 are conducted *in vitro.*

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[16] Claims 9-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

Claims 9-11 are drawn to a method for identifying an agent that interacts with an active site of BACE by determining a genus of active sites of BACE using the relative structural coordinates of Figure 1 ± a root mean square deviation...of not more than 1.5, 1.0, or 0.5 Å. Claims 12-27 are drawn to a method for identifying an agent that interacts with an active site of an APP binding protein or peptide by generating a 3-D model of a genus of active sites of an APP binding protein or peptide using the relative structural coordinates of Figure 1 of the residues recited in claims 12 and 20 ± a root mean square deviation...of not more than 1.5, 1.0, or 0.5 Å, and optionally obtaining or synthesizing the agent and contacting the agent with the APP binding protein or peptide.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the

claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. In this case, the genus of recited active sites encompasses species that are widely variant, including active sites of structural coordinates of mutants and homologs of human BACE from any source, including mutants having function other than BACE or no function at all. The genus of recited agents encompasses agents having any structure, including small organic molecules and peptides that have the ability to bind to proteins other than BACE having the structural coordinates as set forth at Figure 1. It is well-established in the prior art that proteins having similar structure can have different functions (see, *e.g.,* Hegyi et al. *J Mol Biol* 288:147-164). Also, it is known in the art that proteins other than BACE can bind APP (see, *e.g.,* Sheidig et al. *Prot Sci* 6:1806-1824; cited in the IDS filed April 19, 2002). When there is substantial variation within the genus, MPEP § 2163 states one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only two representative species of active sites, *i.e.,* the active site residues as disclosed at Table 1 of human BACE having the structural coordinates of Figure 1 (p. 21) and only a single representative species of agents that interact with BACE or an APP binding protein or peptide that can be obtained or synthesized, *i.e.,* the BACE peptide inhibitor as shown in the specification at p. 6, ¶ [0018]. The specification fails to describe any additional representative species of active sites or agents as encompassed by the claims. As such, the disclosure of the representative species of active sites and the disclosure of

the single species of agents is insufficient to be representative of the attributes and features of all species encompassed by the recited genus of active sites or agents.

Given the lack of description of a representative number of candidate modulators or potential inhibitors, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[17] Claims 9-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an agent that interacts with an active site of the BACE having the structural coordinates of Figure 1, wherein the active site residues are those listed in Table 1 at p. 21 of the specification, and optionally obtaining or synthesizing the BACE inhibitor peptide shown at p. 6, ¶ [0018] of the specification, does not reasonably provide enablement for all methods for identifying an agent that interacts with an active site of BACE by determining an active site of BACE from a 3-D model of BACE using the relative structural coordinates of Figure 1 ± a root mean square deviation...of not more than 1.5, 1.0, or 0.5 Å or all methods for identifying an agent that interacts with an active site of an APP binding protein or peptide by generating a three dimensional model of an active site of an APP binding protein or peptide using the relative structural coordinates of Figure 1 ± a root mean square deviation...of not more than 1.5, 1.0, or 0.5 Å, and optionally obtaining or synthesizing any agent that interacts therewith and contacting the agent with the APP binding protein or peptide, or obtaining or synthesizing any agent that is "designed" by performing such methods as encompassed by the claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

(A) The breadth of the claims: Claims 9-11 are so broad as to encompass methods that require the determination of an active site of BACE from a 3-D model of BACE using the structural coordinates of Figure 1 or variants thereof as encompassed by the claims. The active site of the "BACE" (defined at p. 5, ¶ [0016] of the specification) may be based on structural coordinates of proteins that are structurally related to BACE, but are non-functional and includes proteins having "BACE" function that vary significantly from the structure of the BACE used in the determination of the structural coordinates of Figure 1. Claims 12-27 are even broader as the claims encompass methods that require generating a 3-D model of an active site of any "APP binding protein or peptide" using the structural coordinates of Figure 1 of residues recited in claims 12 and 20. Similarly, the active site of the "APP binding protein or peptide" may be based on structural coordinates of proteins that are structurally related

to BACE, but are non-functional, includes proteins having "BACE" function that vary significantly from the structure of the BACE used in the determination of the structural coordinates of Figure 1, and in this case, includes proteins that are not required to have "BACE" function that have similar or, alternatively, very different structure relative to the BACE having the structural coordinates of Figure 1. Also, claims 16, 19, 24, and 27 include steps of obtaining or synthesizing any agent having any structure that is obtained by the broad scope of claimed methods. The scope of the claims is not commensurate in scope with the enablement provided by the specification.

(B) The nature of the invention: Applicants have crystallized the human BACE (also commonly known as memapsin and beta-secretase) having the amino acid sequence of Figure 1 and have disclosed the structural coordinates of BACE as shown in Figure 1. Using the structural coordinates of BACE, applicants have determined the residues within 4 or 8 Å of an inhibitor peptide were determined (see p. 21 of the specification), which are asserted to be the residues of the APP binding site of BACE (pp. 2-3, ¶¶ [0007]-[0008]). Applicants prophetically utilize the structural coordinates of Figure 1, particularly the alleged residues of the APP binding site of BACE for methods of *in silico* identification of an agent that interacts with the BACE having structural coordinates of Figure 1. Applicants' invention is to use these structural coordinates as disclosed in Figure 1 to identify an agent that interacts with an active site of BACE or an APP binding protein or peptide. Other than claims 16, 19, 24, and 27, the "experimentation" is performed using a computer workstation.

(C) The state of the prior art; (D) The level of one of ordinary skill; and (E) The level of predictability in the art: At the time of the invention, *in silico* screening methods for identifying agents that bind to a defined active site, *e.g.,* the active sites defined in Table 1 at p. 21 of the specification, were known in the art (see p. 12, ¶ [0036] of the specification). However, at the time of the invention, it was highly unpredictable as to whether a variation of an active site based on a known active site, *e.g.,* the active sites as shown in Table 1 of the structural coordinates of Figure 1 ± a root mean square deviation...of not more than 1.5, 1.0, or 0.5 Å, could be used for such screening methods because multiple possible active sites may exist. If the active site was not confirmed prior to *in silico* screening, the possible binding compounds may not have interaction with the protein of interest. Also, it is highly unpredictable as to whether an agent that is identified as binding to variants of the structural coordinates of the BACE having structural coordinates of Figure 1 as encompassed by the claims will also bind to the active site of the BACE having the structural coordinates of Figure 1 as the contacts between the variant and the agent may not be the same as contacts between the active site residues of the BACE having the structural coordinates of Figure 1 and the agent. Further, at the time of the invention, it was highly unpredictable as to whether an active site generated for one protein would be useful for identifying binding agents of another protein, *e.g.,* the use of an active site of BACE for identifying agents that bind to any other APP binding protein or peptide. This unpredictability is evidenced by the disclosure of Hong et al. (*Science* 290:150-153; cited in the IDS filed April 19, 2002), which teaches the crystal structure of BACE in complex with an inhibitor peptide. Hong

et al. disclose, "[t]he protease residues [of BACE] in contact with individual inhibitor side chains...are, however, quite different compared with other aspartic proteases." It is noted that the reference of Hong et al. was made publicly available only after the filing of the instant application.

(F) The amount of direction provided by the inventor and (G) The existence of working examples: In this case, the specification fails to disclose even a single working example of the claimed invention, *i.e.,* the specification fails to actually practice the claimed method for identification of a single compound that can be identified by the claimed method, obtained or synthesized by the claimed method, and used in an *in vitro* binding assay. However, as the alleged APP peptide binding site of BACE is based on an actual 3-D model of BACE co-complexed with a BACE inhibitor peptide, at the time of the invention, one of skill in the art would have recognized that these amino acids are involved in the binding of the inhibitor peptide, *i.e.,* identification of the active site amino acids for binding the inhibitor peptide is correct, and would have an expectation of success for using a model of the active site residues for identifying compounds that bind to that active site. However, the specification fails to disclose any other active site residues of other BACE polypeptides or other APP binding proteins or peptides. Also, regarding claims 16, 19, 24, and 27, it is noted that, other than the peptide inhibitor as shown at p. 6, ¶ [0018], the specification fails to disclose any other working examples of inhibitors that are likely to bind to the BACE active site.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: As stated above, while methods of *in silico* screening to

identify potential binding agents were known in the art at the time of the invention, it was not routine in the art to practice such methods using all active sites as encompassed by the claims to identify compounds having any structure and to obtain or synthesize such compounds, particularly in view of the broad scope of the claims, the lack of guidance and working examples, and the high level of unpredictability in the art.

Thus, in view of the lack of guidance and working examples provided in the specification, the high level of unpredictability, and the significant amount of experimentation required, undue experimentation would be necessary for a skilled artisan to make and use the claimed invention. As such, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). See Case 7 of the "Report on comparative study on protein 3-dimensional (3-D) structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" at www.uspto.gov/web/tws/wm4/wm4_index.htm.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

[18] Claims 9-15, 17-18, 20-23, and 25-26 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Sauder et al. (*J Mol Biol* 300:241-248; "Sauder;" cited in the IDS filed April 19, 2002). The claims are drawn to a method for identifying an agent that interacts with an active site of BACE or a method for identifying an agent that interacts with an active site of an APP binding protein or peptide.

The reference of Sauder teaches a method of computer modeling of human BACE with APP and APP-derived substrates using SCWRL to determine the substrate specificity of BACE (see pp. 244-246). Sauder particularly discloses amino acids that are involved in the interaction of BACE and APP and APP-derived substrates (p. 246). Sauder et al. teach "[i]nhibitors that bind to the BACE active site may prove useful for drugs to treat and prevent Alzheimer's disease" (abstract).

It is noted that the examiner has no way to overlay the BACE active site of Sauder et al. with the active site of BACE as encompassed by the claims or to overlay

the BACE 3-D model of Sauder et al. with a 3-D model of an active site of an APP binding protein or peptide as encompassed by the claims. As such, the examiner has no way to determine whether the BACE 3-D model or active site of Sauder et al. is the same as the active site of BACE or the 3-D model of an active site of an APP binding protein or peptide as encompassed by the claims. However, since the BACE protein used by Sauder et al. appears to be the same as that used in the instant application and there are no disclosed or recited characteristics that would distinguish the method of Sauder et al. from the instantly claimed method, the reference of Sauder et al. anticipates or makes obvious claims 14, 17-18, 21, and 24-28 as written.

Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (*i.e.*, the method of the prior art does not possess the same material characteristics as the claimed method). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

[19] Claims 9-27 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tang et al. (US Patent 6,545,127; "Tang;" cited in the IDS filed October 29, 2003). The claims are drawn to a method for identifying an agent that interacts with an active site of BACE or a method for identifying an agent that interacts with an active site of an APP binding protein or peptide.

The reference of Tang teaches crystallization of human BACE (referred to as memapsin 2 by Tang) co-complexed with a BACE inhibitor (Example 9), determination

of the 3-D structure of human BACE (Example 9), a description of BACE active site residues involved in the binding of the inhibitor (Example 9, Figures 8-13) and a method of computer-assisted rational drug design using the 3-D structure obtained thereby (columns 13-14, Example 10). Tang teaches the design of BACE inhibitors using data obtained from crystal structure data, synthesis of BACE inhibitors so designed (Example 7), and inhibition of BACE using the synthesized inhibitors (Example 8).

It is noted that the examiner has no way to overlay the BACE active site of Tang et al. with the active site of BACE as encompassed by the claims or to overlay the BACE 3-D model of Tang et al. with a 3-D model of an active site of an APP binding protein or peptide as encompassed by the claims. As such, the examiner has no way to determine whether the BACE 3-D model or active site of Tang et al. is the same as the active site of BACE or the 3-D model of an active site of an APP binding protein or peptide as encompassed by the claims. However, since the BACE protein used by Tang et al. appears to be the same as that used in the instant application and there are no disclosed or recited characteristics that would distinguish the method of Tang et al. from the instantly claimed method, the reference of Tang et al. anticipates or makes obvious claims 14, 17-18, 21, and 24-28 as written.

Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (*i.e.*, the method of the prior art does not possess the same material

characteristics as the claimed method). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[20] Claim(s) 9-15, 17-18, 20-23, and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balaji et al. (US Patent 5,579,250; "Balaji") in view *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983). The claims are drawn to a method for identifying an agent that interacts with an active site of BACE or a method for identifying an agent that interacts with an active site of an APP binding protein or peptide.

Balaji teaches methods of rational drug design via computer modeling. Specifically, columns 11-32 detail the use of atomic coordinates of a receptor - such as a protein - wherein drugs or compounds which interact therewith are designed using structural coordinate data obtained from, *e.g.,* X-ray crystallography. Polypeptide modeling is specifically discussed in column 24, line 50, through column 25, line 26. In columns 11-32, energy minimization, bond angles, etc. are discussed as parameters in said design methods. These descriptions are the instant methods, only missing the specific structural coordinates as disclosed in Figure 1.

In *Gulack,* the court held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the computer algorithm used to identify compounds that may bind BACE is a known algorithm and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. In this case, the BACE structural coordinates as disclosed in Figure 1 are nonfunctional descriptive material and the method uses a known unmodified computer algorithm. Data, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. A method of using a known comparator for its known purpose to compare data sets does not become nonobvious merely because new data becomes available for analysis. Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. See MPEP 2106 and Cases 6-7 of the "Report on comparative study on protein 3-dimensional (3-D) structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" at www.uspto.gov/web/tws/wm4/wm4_index.htm.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to perform rational drug design as taught by Balaji to result in an agent that interacts with BACE, wherein only nonfunctional descriptive material is

additionally present in the claims, which do not distinguish the claimed methods from Balaji according to *In re Gulack.*

Conclusion

[21] Status of the claims:

Claims 1-30 are pending.

Claims 1-8 and 28-30 are withdrawn from consideration.

Claims 9-27 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Thursday and alternate Fridays from 7:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (571) 273-8300. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

01-20-05

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